

PATENT/Docket No. PC11050A
Appl. No. 09/989,933
Filing Date: November 21, 2001

Amendments to the Specification:

1. Please replace lines 27-34 on page 2 with the following amended paragraph:

~~U.S. Patent Application Serial Number 08/107,908 has~~ US Patent Nos. 6,168,942, 6,410,032 and 6,410,299 have described that the N^{pro} coding sequence or the N^{pro} protein of BVDV is not required for virus replication. ~~The application has~~ These patents have described the generation of an attenuated BVD virus, "BVDdN1", in which the entire coding sequence for the N^{pro} protein has been deleted from the viral genome. BVDdN1 is infectious in tissue culture and elicits virus neutralizing serum antibodies when vaccinated into cows. Although BVDdN1 can be used as a vaccine against BVDV, BVDdN1 grows in tissue culture at a rate 2-log slower than the parent wild type virus, making the large-scale production of BVDdN1 difficult.

2. Please replace lines 13-23 on page 5 with the following amended paragraph:

It has been shown in ~~the co-pending U.S. Patent Application Serial No. 08/107,908,~~ US Patent Nos. 6,168,942, 6,410,032 and 6,410,299 that the N^{pro} coding sequence or the N^{pro} protein of BVDV is not essential for replication of the virus. An attenuated BVDV virus ("BVDdN1") has been described therein which carries a deletion of the full coding sequence for N^{pro} in the viral genome. BVDdN1 is less infectious than the parent wild type virus and elicits virus neutralizing serum antibodies when vaccinated into cows. The entire disclosure of ~~U.S. Patent Application Serial No. 08/107,908 is~~ US Patent Nos. 6,168,942, 6,410,032 and 6,410,299 are incorporated herein by reference. Although BVDdN1 can be used as a vaccine against BVDV, BVDdN1 grows in tissue culture at a rate about 2-log slower than the parent wild type virus, making the large-scale production of BVDdN1 difficult. Furthermore, the attenuated BVD virus of the present invention replicates faster than BVDdN1 which provides higher immunogenicity for protection.

3. Please replace lines 16-20 on page 13 with the following amended paragraph:

The vaccine compositions of the present invention can also include additional active ingredient such as other vaccine compositions against BVDV, e.g., those described in

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~~co~~pending Application Serial No. ~~08/107,908~~, U.S. Patent No. 6,168,942, U.S. Patent No. 6,410,032, U.S. Patent No. 6,410,299, WO 9512682, WO 9955366, U.S. Patent No. 6,060,457, U.S. Patent No. 6,015,795, U.S. Patent No. 6,001,613, and U.S. Patent No. 5,593,873, all of which are incorporated by reference in their entirety.

4. Please replace lines 6-13 on page 15 with the following amended paragraph:

The DNA sequence of bovine polyubiquitin has been described by Meyers, G., et al. (*Virology*:180, 602-616, 1991) and is present in GenBank (BOVPOUBA, Accession # M62429 M37794). Cloning and introduction of a monomeric ubiquitin into vector pvvNADLd1NS2 involved two rounds of PCR amplification and synthesis of three PCR fragments. Plasmid pvvNADLd1NS2 is a derivative of pvvNADL (an infectious clone of BVDV described in ~~U.S. Patent Application Serial No. 08/107,908~~ U.S. Patent No. 6,168,942, U.S. Patent No. 6,410,032, and U.S. Patent No. 6,410,299) in which the coding region of NS2 is deleted. In the first round, PCR fragments 1 and 2 were generated which then served as templates for the second round of PCR amplification resulting in PCR fragment 3 (Figure 1A).

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